Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1-20. (Cancelled).

21. (Currently amended) A method for obtaining an agent for alleviating pain, the method comprising:

(a) producing a genetic construct having nucleic acids encoding a clostridial neurotoxin;

(b) incorporating the construct into a host cell;

(c) culturing the cell under conditions sufficient to express the clostridial neurotoxin; and

(d) covalently attaching ~~or recombinantly fusing~~ the clostridial neurotoxin to a targeting moiety which comprises substance P, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction.

22. (Original) The method of claim 21, wherein the covalent linkage includes one or more spacer components.

23-35. (Cancelled)

36. (Previously presented) A plasmid encoding a clostridial neurotoxin, comprising:

(a) a first nucleotide sequence comprising; (i) a first nucleotide segment encoding an amino acid sequence comprising a targeting moiety of substance P able to specifically bind to receptors on cells under physiological conditions; and (ii) a second nucleotide segment encoding an amino acid sequence comprising a translocation element able to facilitate the transfer of a polypeptide across an endosome membrane; and

(b) a second nucleotide sequence encoding an amino acid sequence comprising a therapeutic element having an intracellular protease biological activity when released into the cytoplasm of a target cell, and an element for replication directing plasmid replication by a host cell, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction.

37. (Previously presented) A method of making a clostridial neurotoxin comprising:

(a) inserting the plasmid of claim 36 into a suitable host cell,

(b) culturing the host cell under conditions sufficient to express the clostridial neurotoxin, and

(c) isolating the clostridial neurotoxin.

38-66. (Cancelled)

67. (Previously presented) A method for obtaining an agent for alleviating pain, the method comprising:

(a) producing a genetic construct having nucleic acids encoding a clostridial neurotoxin;

(b) incorporating the construct into a host cell;

(c) culturing the cell under conditions sufficient for expression of the clostridial neurotoxin; and

(d) covalently attaching the expressed clostridial neurotoxin to substance P, wherein H_C has been removed from the clostridial neurotoxin or modified so as to reduce the ability of the clostridial neurotoxin to bind to a receptor for the H_C at a neuromuscular junction.

68. (Previously presented) The method of claim 67, further comprising covalently attaching at least one spacer component between the clostridial neurotoxin and the substance P.

69. (Currently amended) The method of claim 67, wherein the expressed clostridial neurotoxin has an amino acid sequence substantially identical to a neurotoxin from an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

70. (Previously presented) The method of claim 67, wherein the expressed clostridial neurotoxin has an amino acid sequence substantially identical to a botulinum toxin selected from the group consisting of serotype A, serotype B, serotype C1, serotype D, serotype E, serotype F, and serotype G.

71. (Previously presented) The method of claim 67, wherein the expressed clostridial neurotoxin has an amino acid sequence substantially identical to botulinum toxin serotype A.

72. (Previously presented) The method of claim 67, wherein the clostridial neurotoxin comprises an H_N and an L chain.

73. (Previously presented) The method of claim 72, wherein the H_N is a translocation domain of a clostridial neurotoxin having an amino acid sequence substantially identical to a clostridial neurotoxin from an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

74. (Previously presented) The method of claim 72, wherein the L chain is a light chain of a clostridial neurotoxin having an amino acid sequence substantially identical to a clostridial neurotoxin from an organism selected from the group consisting of Clostridial beratti, Clostridial butyricum, Clostridial botulinum, and Clostridial tetani.

75. (Previously presented) The method of claim 72, wherein the H_N is a translocation domain having an amino acid sequence substantially identical to a translocation domain of a botulinum toxin selected from the group consisting of botulinum toxin serotype A, serotype B, serotype C1, serotype D, serotype E, serotype F, and serotype G.

76. (Cancelled)

77. (Previously presented) A method for obtaining an agent for alleviating pain, the method comprising:

(a) producing a genetic construct having nucleic acids encoding a botulinum toxin serotype A;

(b) incorporating the construct into a host cell;

(c) culturing the cell under conditions sufficient for expression of the botulinum toxin serotype A; and

(d) covalently attaching the botulinum toxin serotype A to substance P, wherein H_c has been removed from the botulinum toxin or modified so as to reduce the ability of the botulinum toxin to bind to a receptor for the H_c at a neuromuscular junction.

78. (Previously presented) A method for obtaining an agent for alleviating pain, the method comprising:

(a) producing a genetic construct having nucleic acids encoding a botulinum toxin, wherein the nucleotide sequence encoding an Hc of the toxin has been removed;

(b) incorporating the construct into a host cell;

(c) culturing the cell under conditions sufficient for expression of the botulinum toxin; and

(d) covalently attaching the botulinum toxin to substance P.

79-80. (Cancelled)